Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838.

Roskelley, C. D.; Williams, D. E.; McHardy, L. M.; Leong, K. G.; Troussard, A.; Karsan, A.; Andersen, R. J.; Dedhar, S.; Roberge, M. *Cancer Res.* **2001**, *61*, 6788.

Williams, D. E.; Craig, K. S.; Patrick, B.; McHardy, L. M.; van Soest, R.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2002**, *67*, 245.

Wakabayashi, T.; Kageyama, R.; Naruse, N.; Tsukahara, N.; Funahashi, Y.; Kitoh, K.; Watanabe, Y. *J. Antibiot.* **1997**, *50*, 671.

Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458.

Jung, H. J.; Lee, H. B.; Kim, C. J.; Rho, J. R.; Shin, J.; Kwon, H. J. *J. Antibiot.* **2003**, *56*, 492.

Tatsuta, K.; Masuda, N. *J. Antibiot.* **1998**, *51*, 602.

Myers, A. G.; Siu, M.; Ren, F. *J. Am. Chem. Soc.* **2002**, *124*, 4230.

Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514.

Nakae, K.; Yoshimoto, Y.; Sawa, T.; Homma, Y.; Hamada, M.; Takeuchi, T.; Imoto, M. *J. Antibiot.* **2000**, *53*, 1130.

Nakae, K.; Yoshimoto, Y.; Ueda, M.; Sawa, T.; Takahashi, Y.; Naganawa, H.; Takeuchi, T.; Imoto, M. *J. Antibiot.* **2000**, *53*, 1228.

Takemoto, Y.; Nakae, K.; Kawatani, M.; Takahashi, Y.; Naganawa, H.; Imoto, M. *J. Antibiot.* **2001**, *54*, 1104.

Nakamura, H.; Takahashi, Y.; Naganawa, H.; Nakae, K.; Imoto, M.; Shiro, M.; Matsumura, K.; Watanabe, H.; Kitahara, T. *J. Antibiot.* **2002**, *55*, 442.

Woo, E. J.; Starks, C. M.; Carney, J. R.; Arslanian, R.; Cadapan, L.; Zavala, S.; Licari, P. *J. Antibiot.* **2002**, *55*, 141.

Mattson, M. P.; Furukawa, K. *Apoptosis* **1997**, *2*, 257.

Kondo, H.; Oritani, T.; Kiyota, H. *Eur. J. Org. Chem.* **2000**, 3459.

D'Amato, R. J.; Loughnan, M. S.; Flynn, E.; Folkman, J. *Proc. Natl. Acad. Sci.* **1994**, *91*, 4082.

Thomas, D. A.; Kantarjian, H. M. *Curr. Opin. Oncol.* **2000**, *12*, 635.

Raje, N.; Anderson, K. C. *Curr. Opin. Oncol.* **2002**, *14*, 635.

Dredge, K; Dalgleish, A. G.; Marriott, J. B. *Anti-Cancer Drugs* **2003**, *14*, 331.

Capitosti, S. M; Hansen, T. P.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 327.

Sugawara, K.; Nishiyama, Y.; Toda, S.; Komiyama, N.; Halori, M.; Moriyama, T.; Sawada, Y.; Kamei, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1433.

Karwowski, J. P.; Jackson, M.; Sunga, G.; Sheldon, P.; Poddig, J. B.; Kohl, W. L.; Adam, S. *J. Antibiot.* **1994**, *47*, 862.

Hochlowski, J. E.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1994**, *47*, 870; Kadam, S.; McAlpine, J. B. *J. Antibiot.* **1994**, *47*, 875.

Takayasu, Y.; Tsuchiya, K.; Aoyama, T.; Sukenaga, Y. *J. Antibiot.* **2001**, *54*, 1111.

Takayasu, Y.; Tsuchiya, K.; Sukenaga, Y. *J. Antibiot.* **2002**, *55*, 337.

Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042.

Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038.

Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59; Danishefsky, S. J. *Chemtracts* **1989**, *2*, 273.

Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 9039.

Xiang, G.; McLaughlin, L. W. *Tetrahedron* **1998**, *54*, 375.

Kitaori, K.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Tetrahedron* **1999**, *55*, 14381.

Reetz, M. T.; Kessler, K. *J. Org. Chem.* **1985**, *50*, 5434.

Danishefsky, S. J.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry Jr., P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.

Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

Ahmar, M.; Duyck, C.; Fleming I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2721.

Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H *Tetrahedron Lett.* **1999**, *40*, 2247.

Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297.

Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825.

Jorgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630.

Lee, W. W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473.

Danishefsky, S. J.; Kato, N.; Askin, D.; Kerwin Jr., J. F. *J. Am. Chem. Soc.* **1982**, *104*, 360.

Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2279.

Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

Edmonds, M. K.; Abell, A. D. *J. Org. Chem.* **2001**, *66*, 3747; Smith III, A. B.; Frohn, M. *Org. Lett.* **2001**, *3*, 3979.

Egawa, Y.; Suzuki, M.; Okuda, T. *Chem. Pharm. Bull.* **1963**, *11*, 589.

Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. M.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* 1979, *52*, 1989.

Song, F.; Fidanze, S.; Benowitz, A. B.; Kishi, Y. *Org. Lett.* 2002, *4*, 647.

Mukaiyama, T., Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* 1975, 1045.

Mukaiyama, T. *Angew. Chem. Int. Ed.* 1979, *18*, 707.

Boden, E. P.; Keck, G. E. *J. Org. Chem.* 1985, *50*, 2394.

Stachel, S. J.; Lee, C. B.; Spassova, M.; Chappell, M. D.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* 2001, *66*, 4369.

Chun, J.; Li, G.; Byun, H. S.; Bittman, R. *J. Org. Chem.* 2002, *67*, 2600.

Dixon, D. J.; Krause, L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1*, 2001, 2516.

Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* 1994, *59*, 4202.

Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Tetrahedron* 1997, *53*, 8541.

Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* 2000, *11*, 2781.

Li, D. R.; Xia, W. J.; Shi, L.; Tu, Y. Q. *Synthesis* 2004, 41.

Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* 1989, *111*, 393.

All patents and publications referenced or mentioned herein are indicative of the levels of skill of those skilled in the art to which the invention pertains, and each such referenced patent or publication is hereby incorporated by reference to the same extent as if it had been incorporated by reference in its entirety individually or set forth herein in its entirety. Applicants reserve the right to physically incorporate into this specification any and all materials and information from any such cited patents or publications.

The specific methods and compositions described herein are representative of preferred embodiments and are exemplary and not intended as limitations on the scope of the invention. Other objects, aspects, and embodiments will occur to those skilled in the art upon consideration of this specification, and are encompassed within the spirit of the invention as defined by the scope of the claims. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The

invention illustratively described herein suitably may be practiced in the absence of any element or elements, or limitation or limitations, which is not specifically disclosed herein as essential. The methods and processes illustratively described herein suitably may be practiced in differing orders of steps, and that they are not necessarily restricted to the orders of steps indicated herein or in the claims. As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality (for example, a culture or population) of such host cells, and so forth. Under no circumstances may the patent be interpreted to be limited to the specific examples or embodiments or methods specifically disclosed herein. Under no circumstances may the patent be interpreted to be limited by any statement made by any Examiner or any other official or employee of the Patent and Trademark Office unless such statement is specifically and without qualification or reservation expressly adopted in a responsive writing by Applicants.

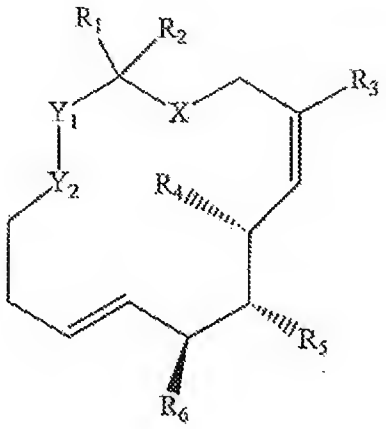
The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intent in the use of such terms and expressions to exclude any equivalent of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention as claimed. Thus, it will be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

WHAT IS CLAIMED:

1. A composition for treating or preventing metastatic cancer in a mammal comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula I:



wherein:

X is CH, N, NH or O;

R_1 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_2 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_3 is H or lower alkyl;

R_4 is H or lower alkyl;

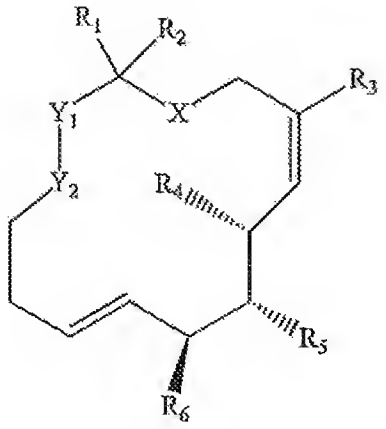
R_5 is OH;

R_6 is alkyloxy;

Y_1 and Y_2 are separately $-CH_2-$ or Y_1 and Y_2 together form –C=C–;

or a pharmaceutically acceptable salt thereof.

2. A composition for treating or preventing migration of a mammalian cell comprising a carrier and an effective amount of a compound of formula I:



wherein:

X is CH, N, NH or O;

R_1 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_2 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_3 is H or lower alkyl;

R_4 is H or lower alkyl;

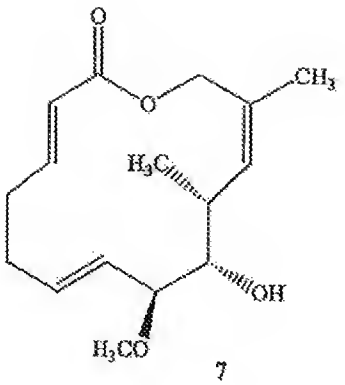
R_5 is OH;

R_6 is alkyloxy;

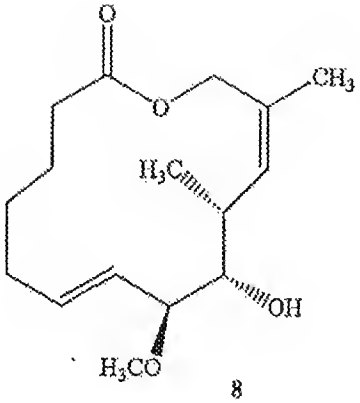
Y_1 and Y_2 are separately $–CH_2–$ or Y_1 and Y_2 together form –C=C–;

or a pharmaceutically acceptable salt thereof.

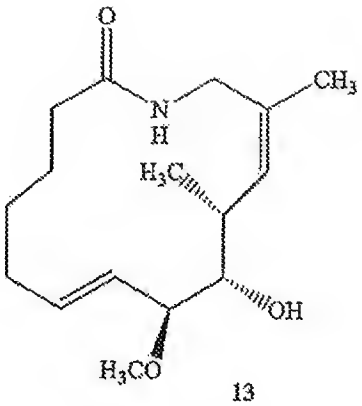
3. The composition of claim 1 or 2, wherein the compound is any one of the following compounds:



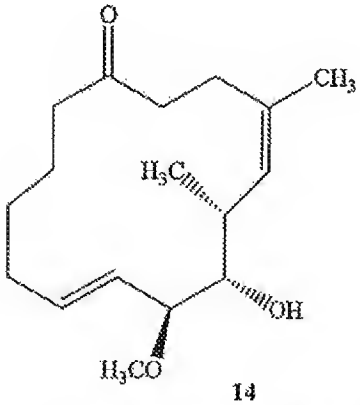
7



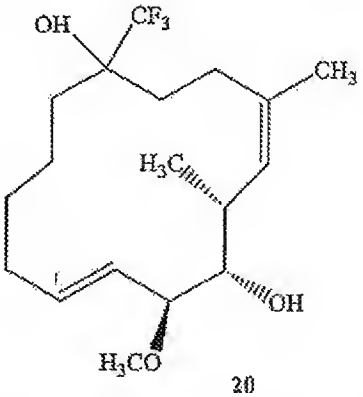
8



13



14

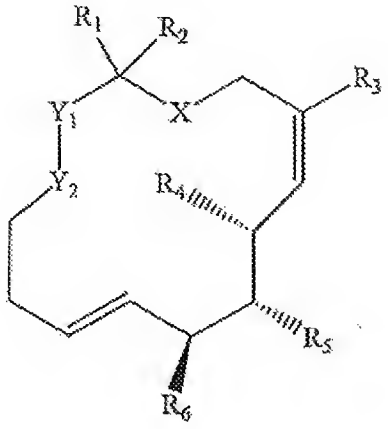


20

4. The composition of claim 1 or 2, wherein the effective amount of the compound is about 1.0 mg/kg to about 200 mg/kg.

5. The composition of claim 1 or 2, wherein the effective amount of the compound is about 5 mg/kg to about 20 mg/kg.

6. A method of inhibiting migration of a mammalian cell comprising contacting the mammalian cell with a compound of formula I:



wherein:

X is CH, N, NH or O;

R_1 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_2 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_3 is H or lower alkyl;

R_4 is H or lower alkyl;

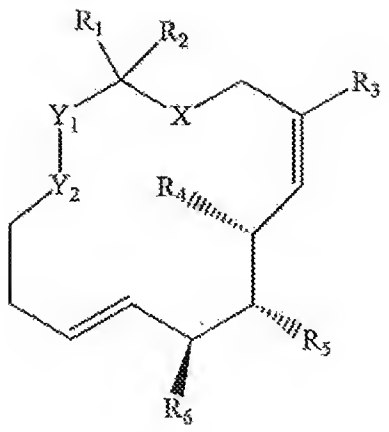
R_5 is OH;

R_6 is alkyloxy;

Y_1 and Y_2 are separately $-CH_2-$ or Y_1 and Y_2 together form –C=C–;

or a pharmaceutically acceptable salt thereof.

7. A method of inhibiting metastasis of a cancer cell in a mammal comprising administering to the mammal a therapeutically effective amount a compound of formula I:



wherein:

X is CH, N, NH or O;

R_1 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_2 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_3 is H or lower alkyl;

R_4 is H or lower alkyl;

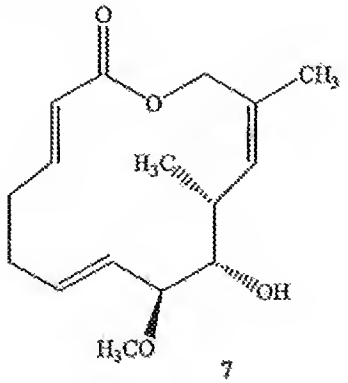
R_5 is OH;

R_6 is alkyloxy;

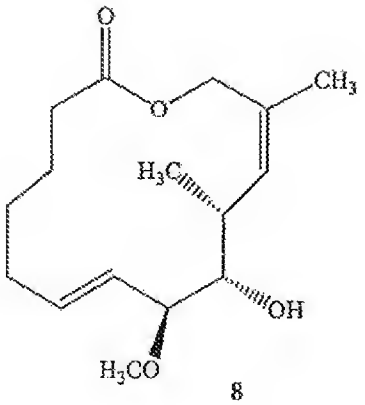
Y_1 and Y_2 are separately $-CH_2-$ or Y_1 and Y_2 together form –C=C–;

or a pharmaceutically acceptable salt thereof.

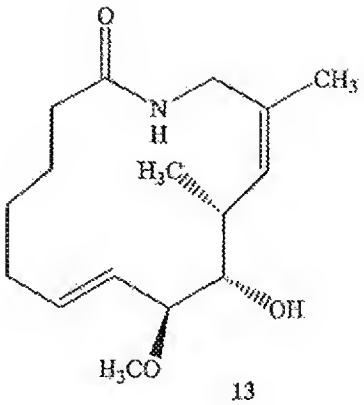
8. The method of claim 6 or 7, wherein the compound is any one of the following compounds:



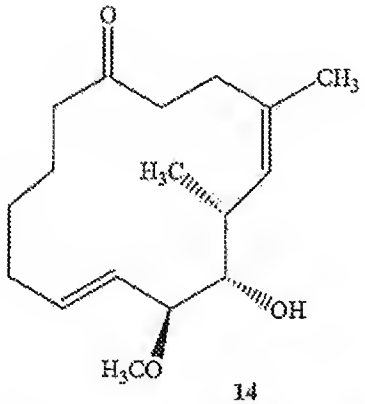
7



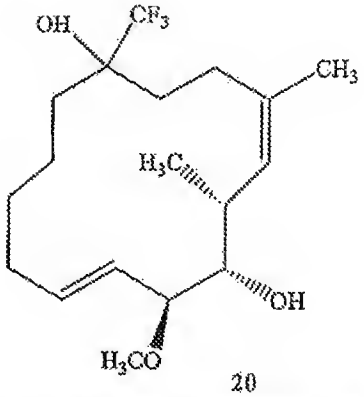
8



13



14



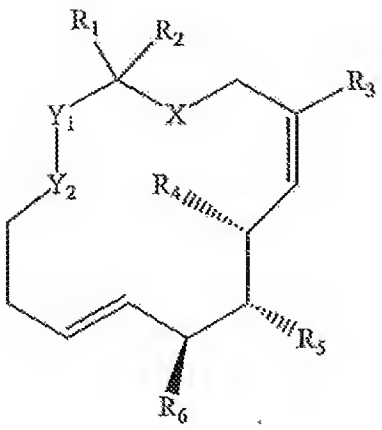
20

9. The method of claim 6 or 7, wherein the effective amount of the compound is about 1.0 mg/kg to 200 mg/kg.

10. The method of claim 6 or 7, wherein the effective amount of the compound is about 5 mg/kg to about 20 mg/kg.

11. The method of claim 6 or 7, wherein the mammal is a human.

12. The use of a compound of formula I for the manufacture of a medicament useful for the treatment of metastatic cancer in a mammal:



wherein:

X is CH, N, NH or O;

R_1 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_2 is OH, CZ_3 or R_1 and R_2 together are –C=O, wherein Z is halo;

R_3 is H or lower alkyl;

R_4 is H or lower alkyl;

R_5 is OH;

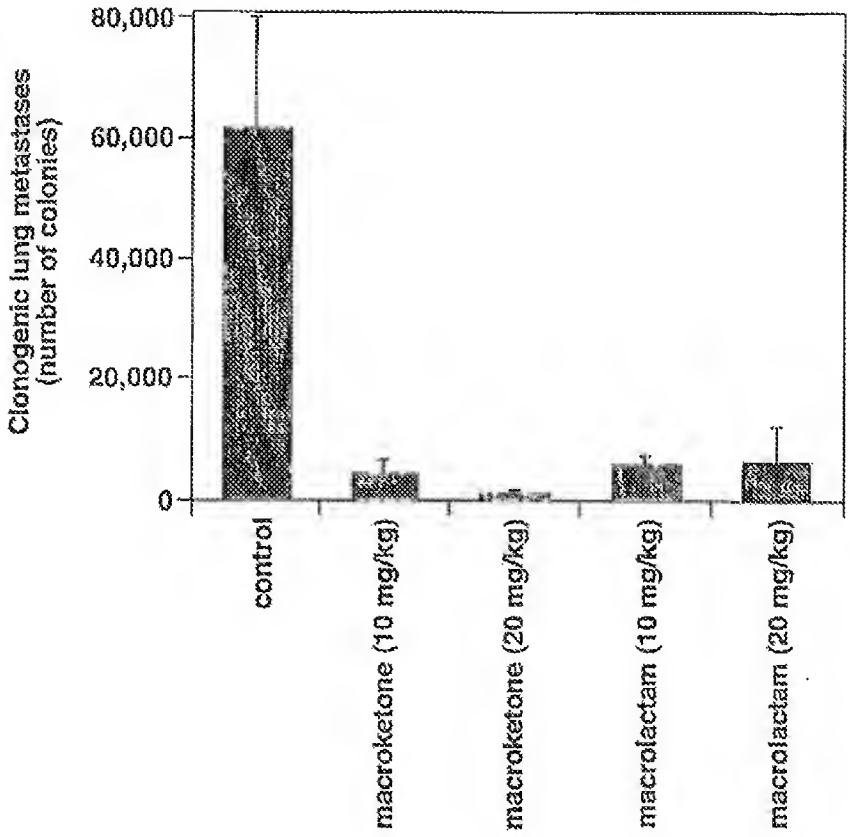
R_6 is alkyloxy;

Y_1 and Y_2 are separately $-CH_2-$ or Y_1 and Y_2 together form –C=C–;

or a pharmaceutically acceptable salt thereof.

13. The use of claim 12, wherein the mammal is a human.

Figure 1


Clonogenic lung metastases (number of colonies)
80,000
60,000
40,000
20,000
0
control
macroketone (10 mg/kg)
macroketone (20 mg/kg)
macrolactam (10 mg/kg)
macrolactam (20 mg/kg)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009211

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D225/02 C07D313/00 C07C13/02 A61K31/365 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAUL C ET AL: "Synthesis of the macrolide core of migrastatin" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 50, 9 December 2002 (2002-12-09), pages 9039-9042, XP004391896 ISSN: 0040-4039 cpd. 13 the whole document ----- -/--	1-13

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2004	23/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009211

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"MIGRASTATIN, A NOVEL 14-MEMBERED LACTONE FROM STREPTOMYCES SP, MK929-43F1" JOURNAL OF ANTIBIOTICS, JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO, JP, vol. 53, no. 10, October 2000 (2000-10), pages 1228-1230, XP002938945 ISSN: 0021-8820 cited in the application the whole document	1-13
A	US 2002/119937 A1 (CARNEY JOHN ET AL) 29 August 2002 (2002-08-29) the whole document	1-13

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/009211

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002119937 A1	29-08-2002	NONE	